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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/656,055	09/05/2003	Debbie Yaver	10322.200-US	8946

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EXAMINER	
HINES, JANA A	
ART UNIT	PAPER NUMBER
1645	
MAIL DATE	DELIVERY MODE
09/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/656,055	YAVER ET AL.	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11,36,42,43 and 82-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,11,36,42,43 and 82-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 18, 2007 has been entered.

Amendment Entry

2. The amendment filed on June 2, 2007 has been entered. Claims 1 and 36 have been amended. Claims 2-10, 12-35, 37-41 and 44-81 have been cancelled. Claims 1, 11, 36, 42-43 and 82-93 are under consideration in this office action.

Withdrawal of Rejections

3. The following rejections have been withdrawn in view of applicants' amendments and arguments:

a) The objection of claim 27 under 37 CFR 1.75(c);

b) The rejection of claims 80-81 under 35 U.S.C. 101;

c) The new matter rejection of claims 90-93 under 35 U.S.C. 112, first paragraph; and

d) The rejection of claims 1, 11, 27, 34, 36 and 42 under 35 U.S.C. 103(a) as being unpatentable over Zhang et al., in view of Kunst et al.

Response to Arguments

4. Applicant's arguments filed July 18, 2007 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. The rejection of claims 1, 11, 36, 42 and 43 under 35 U.S.C. 112, second paragraph, is maintained for reasons already of record.

a) The remaining rejection is on the grounds that the term " dissimilarity" in claim 1 is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Neither the claims nor the specification teach the metes and bounds of what is dissimilar. There is no criteria which defines how to determine whether something is dissimilar or not. Thus the claim is unclear and appropriate clarification is required to overcome the rejection.

Applicants' assert that the term "similarity" has been defined on pages 22-23, lines 16-2. The specification is silent as to the determining dissimilarity. There is no definition of an actual amount. The term is a relative term, and therefore is indefinite. Thus the rejection is maintained and applicants' arguments are not persuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 82-87 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Neither the specification nor originally presented claims provides support for the method of determination wherein the plurality of sequences correspond to less than about 75%, 50%, 25%, 10%, 5%, or 2% of the genome of the *B. subtilis* cells. Applicant did not point to support in the specification for a method wherein the plurality of sequences correspond to a percentage of the genome of the *B. subtilis* cells. Moreover, applicant failed to specifically point to the identity of the newly claimed method steps. Therefore it appears that the entire specification appears to fail to recite support for the newly recited method steps. The instantly recited claims are not drawn to microarray based expression profiles with include cluster analysis. Therefore, the claims incorporate new matter. Accordingly, it appears that there is no support in the specification. Therefore, applicants must specifically point to page and line number

support for the identity of the method as recited by the newly added claims. Therefore, the new claims incorporate new matter and are accordingly rejected.

Response to Arguments

7. Applicant's arguments filed July 18, 2007 have been fully considered but they are not persuasive.

Applicants urge that page 13, lines 20-27 provide support for the plurality of sequences correspond to less than about 75%, 50%, 25%, 10%, 5%, or 2% of the genome of the *B. subtilis* cells. However, page 13, lines 20-27 that the sequences represent about 75% of the genome or less, about 50% of the genome or less, about 25% of the genome or less, about 10% of the genome or less, about 5% of the genome or less, or even about 2% of the genome or less. There is no teaching of the sequences corresponding to less than about 75%, 50%, 25%, 10%, 5%, or 2% of the genome of the *B. subtilis* cells. Therefore the rejection is maintained and applicants' arguments are not persuasive.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 82-87 and 90-93 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) The phrase "correspond to less than about 75% of the genome of the *Bacillus subtilis* cells" in claims 82-87 is a relative term which renders the claim indefinite. The phrase is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear how to define "corresponds to". There is no definition for determining what sequences corresponds to the *B. subtilis* genome and which sequences do not correspond. The metes and bounds of determining the correspondence are unclear. It is also unclear how to define, "less than about." Therefore clarification is required to overcome the rejection.

b) Claim 36 recites the limitation "the detected expression level" in the claim. There is insufficient antecedent basis for this limitation in the claim.

c) The phrase "at least about 20, 50, 75 or 100% of the genome of the *Bacillus subtilis* cells" in claims 90-93 is a relative term which renders the claim indefinite. The phrase is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear how to define "at least about". There is no definition for determining what is at least 20% and what is also about 20%. The metes and bounds of determining the difference in the detected

expression levels is unclear. Therefore clarification is required to overcome the rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1, 11, 27, 34, 36 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al., (PNAS, 1999. Vol. 96(22): 12833-12838) in view of Cao et al., (Mol. Microbio. 2002. Vol. 45(5): 1267-1276).

The claims are drawn to a method for determining the mode of action of an antimicrobial compound, comprising: a) detecting hybridization complexes formed by contacting at least one nucleic acid sample, obtained by culturing *Bacillus subtilis* cells in the presence of at least one subinhibitory amount of an antimicrobial compound having an unknown mode of action, with a plurality of nucleic acid sequence corresponding to genes of the *Bacillus subtilis* cells, wherein the plurality of nucleic acid sequences is contained on a substrate, wherein the presence, absence or change in the amount of the hybridization complexes detected, compared with hybridization complexes formed between the plurality of nucleic acid sequences and a second nucleic acid sample obtained from the *Bacillus subtilis* cells cultured in the absence or presence of a standard compound having a known mode action, is indicative of the

similarity or dissimilarity of the mode of actions of the antimicrobial compound and the standard compound; and b) assigning a mode of action for the antimicrobial compound based on the similarity or dissimilarity of values assigned to the hybridization complexes detected in (a) based on the hybridization complexes formed from the second nucleic acid sample. The dependant claims are drawn to action of the antimicrobial compound and the source of the plurality of nucleic acids.

Wilson et al., teach exploring drug-induced alterations in gene expression by microarray hybridization. Wilson et al., teach drugs and compounds selectively induce changes in the transcription of genes, and the resulting gene expression profile would serve as a signature of the inhibitor used especially in cases of inhibitors whose modes of action were unknown (page 12,833). Wilson et al., teach the ability for pathway characterization is available because complete genome sequences are known and microarrays containing representatives of each of the genes are known (page 12,833). Wilson et al., teach the preparation of DNA microarrays which contains genomic sequences and fragments on a substrate (page 12,834). Wilson et al., teach culturing, growth and drug treatment of the bacterial strains with the drug (page 12,834). Wilson et al., teach microarray hybridization where the DNA was applied to the array in a hybridization mixture which allowed hybridization to occur (page 12,835). Wilson et al., teach the detection of hybridization complexes formed by contacting at least one nucleic acid with a plurality of nucleic acid sequences corresponding to genes of the bacterial cells. Wilson et al., teach the microarray hybridization provides a characteristic

signature for the cellular processes that are affected by the compound (page 12,838). Wilson et al., teach the drug response profiles were distinct from the profiles obtained from bacteria exposed in a similar manner to a variety of different compounds (page 12,838).

Wilson et al, teach a generated response to isoniazid (INH), thus the antimicrobial compound is a member of the class of compounds which interferes with the cell membrane. Wilson et al., teach that this system provides the framework for interpreting the transcriptional responses that we would detect by the microarray hybridization and allow for comparison with published results of genes and proteins that are known to be INH induced (page 12,833). Wilson et al., teach the comparison with hybridized complexes formed between the plurality of nucleic acid sequences and a second nucleic acid sample obtained from bacterial cells cultured in the absence or presence of a standard compound having a known mode of action. Wilson et al., teach the profiles provided are indicative of the similarity or dissimilarity of the mode of actions of the antimicrobial compound and the standard compound. Wilson et al., also identified at least one sequence from the genes which encode the KatG complex that has a level significantly different from bacterial cells not in the presence of INH (page 12,837). Wilson et al., teach the results show that the characteristic drug response is the result of intracellular conditions associated with the drugs mode of action (page 12,838). Thus Wilson et al., teach it is possible to predict the mode of action of a novel compound based on a physiologically derived interpretation of its expression response to that compound (page 12,838). Wilson et al., teach the plurality of sequences

corresponding to less than about 75% of the genome of *Bacillus subtilis* cells. However, Wilson et al., do not teach culturing cells of *Bacillus subtilis*.

Cao et al., teach culturing *B. subtilis* strains for DNA microarray analysis (page 1274, col. 2). Cao et al., teach detecting hybridization complexes formed by contacting at least one nucleic acid sample, obtained by culturing *Bacillus subtilis* cells in the presence of at least one subinhibitory amount of an antimicrobial compound having an unknown mode of action, with a plurality of nucleic acid sequence corresponding to genes of the *Bacillus subtilis* cells, wherein the plurality of nucleic acid sequences is contained on a substrate (page 1274, col. 2). Cao et al., teach RNA isolation, cDNA synthesis, slide hybridization and labeling (page 1274, col. 2). Cao et al., teach detecting and quantifying the presence, absence or change in the amount of the hybridization complexes, and comparing with hybridization complexes formed between the plurality of nucleic acid sequences and a second nucleic acid sample obtained from the *Bacillus subtilis* cells cultured in the absence or presence of a standard compound having a known mode action, is indicative of the similarity or dissimilarity of the mode of actions of the antimicrobial compound and the standard compound using data analysis software (page 1274, col.2). Cao et al., teach the induction of many genes (page 1271, col.1). Cao et al., teach comparing *M. tuberculosis* to various antibiotics (page 1273, col.1). Cao et al., teach that *B. subtilis* co-exists with many microorganisms and that Bacillus' antibiotic resistance genes need control (page 1267, col.2).

Therefore it would have been prima facie obvious at the time of applicants' invention to apply the *Bacillus subtilis* strain of Cao et al., to Wilson et al., method for

determining the mode of action of an antimicrobial compound in order to provide obtain antimicrobial mode of action results for *B. subtilis* which is known to be resistant to known antimicrobial drugs. One of ordinary skill in the art would have a reasonable expectation of success by exchanging one gram positive bacterium for another gram positive bacteria because both bacteria are known in the art to have analyzed on DNA microarrays wherein the hybridization complexes detected in the presence of antimicrobial compounds. Furthermore, no more than routine skill would have been required to exchange the *M. tuberculosis* of Wilson et al., for the *B. subtilis* of Cao et al., since the ability for pathway characterization is available because complete genome sequences of *B. subtilis* is known along with microarrays containing representatives of each of the genes. Finally it would have been prima facie obvious to combine the invention of Wilson et al., and Cao et al., to advantageously achieve a determining drug-induced alterations in gene expression by microarray hybridization for multi-drug resistant bacteria.

Conclusion

10. No claims allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Jeffery Siew, can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines
September 17, 2007

MARK NAVARRO
PRIMARY EXAMINER